JC03 Rec'd PCT/PTO 22 JAN 2002 PCT

FORM PTO-1390 (REV. 12-2001) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY 'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	61905/2
	U S APPLICATION NO (If known, see 37 CFR 1 5) 10/031449

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/CA00/00850	07/21/2000	07/21/1999

TITLE OF INVENTION
ASYMMETRIC LIGANDS HAVING USE AS CATALYSTS

APPLICANT(S) FOR DO/EO/US
YUDIN Andrei ; MARTYN, Leo James Patrick ; PANDIARAJU, Subramanian.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information:
    Return Receipt Postcard

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/031449	PCT/CA00/00850	61905/2

21. ☐ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	39 - 20 =	19	x **$18.00**	$ 342	
Independent claims	7 - 3 =	4	x **$84.00**	$ 336	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$ 280	
TOTAL OF ABOVE CALCULATIONS =				$ 1848	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$	
SUBTOTAL =				$	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 924	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 894	
				Amount to be refunded:	$
				charged:	$ 30

a. ☒ A check in the amount of $ 894 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2553. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

SIGNATURE

Brian W. Gray

NAME

30,017

REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	YUDIN, A.; MARTYN, L.J.P. and PANDIARAJU, S.
Serial No.:	PCT/CA00/00850
Int. Filing Date:	July 21, 2000
Title:	Asymmetric Ligands Having use as Catalysts
Art Unit:	
Examiner:	
Atty's Docket No.:	61905/2

The Commissioner of Patents and Trademarks
Washington, D.C. 20331
U.S.A.

Dear Sir:

This is a preliminary amendment to the above referenced application as filed July 21, 2000.

IN THE SPECIFICATION

Please replace the paragraph beginning at line 4 of page 1 of the description with the following rewritten paragraph:

--This application is submitted under 35 U.S.C. 371 from PCT/CA 00/00850 filed July 21, 2000 designating the United States, and claims priority from United States Provisional Patent Application Nos. 60/144, 812 and 60/201,730, filed July 21, 1999 and May 4, 2000, respectively, the specifications of which are hereby incorporated by reference in their entirety. --

IN THE CLAIMS

Please cancel claims 1-59 of the parent application, International Patent Application No. PCT/CA 00/00850, and add the following new claims 60-99:

60. An asymmetric ligand comprising an aromatic ring system that is polyfluorinated.

61. The ligand as claimed in claim 60 wherein the aromatic ring system is in the form of a biphenyl, binaphthyl, bipyridyl ring system, or a derivative thereof.

62. The ligand as claimed in claim 61 wherein the aromatic ring system comprises a binaphthyl derivative.

63. The ligand as claimed in claim 62 wherein the aromatic ring system comprises a 2, 2′ di substituted binaphthyl ring system.

64. The ligand as claimed in claim 63 wherein the substituents at the 2 and 2′ positions are the same or different, and are each OR where R may be:

a) hydrogen; or

b) C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with:

i) N, O, S, or P;

ii) P R′R″ where R′ and R″ are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;

iii) phosphine oxide;

iv) NR′′′ R′′′′ where R′′′ and R′′′′ are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;

v) SR′′′′′ R′′′′′′ where R′′′′′ and R′′′′′′ are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched,

saturated or unsaturated, unsubstituted or substituted with N, O, S, or P.

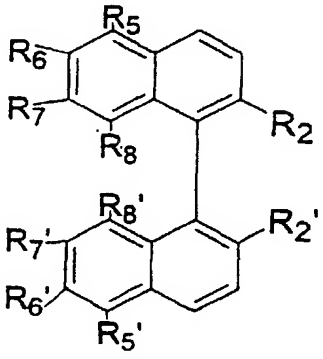
65. The ligand as claimed in claim 64 wherein R is hydrogen, or C_1-C_6 alkyl which is linear or branched.

66. The ligand as claimed in claim 63 wherein the 5, 6, 7, and 8 or the 5′, 6′, 7′ and 8′positions of the binaphthyl ring system are fluorinated.

67. The ligand as claimed in claim 63 wherein the binaphthyl ring system is fluorinated at the 5, 5′, 6, 6′, 7, 7′, 8 and 8′ positions.

68. The ligand as claimed in claim 66 which is selected from the group of ligands comprising 5, 5′, 6, 6′, 7, 7′, 8, 8′-octafluoro-2,2′-dihydroxy-1,1′- binaphthyl, 5, 5′, 6, 6′, 7, 7′, 8, 8′-octafluoro- 2,2′- dimethoxy-1,1′- binaphthyl, 5, 5′, 6, 6′, 7, 7′, 8, 8′-octafluoro-2,2′-di-n-propoxy-1,1′ -binaphthyl and 5, 5′, 6, 6′, 7, 7′, 8, 8′-octaflu oro-2,2′-di-i-propoxy-1,1′ -binaphthyl.

69. An asymmetric compound of the formula III:



wherein R2 and R2′ are the same or different and are OR where R is:

a) Hydrogen;

b) C_1-C_{20} alkyl aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with:

i) N, O, S, or P;

ii) PR'R'' where R' and R'' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;

iii) phosphine oxide;

iv) NR''' R'''' where R''' and R'''' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;

v) SR''''' R'''''' where R''''' and R'''''' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted, or substituted with N, O, S, or P;

and R5, R5', R6, R6', R7, R7', R8 and R8' are independently hydrogen, fluorine, CN, or NO_2, OR (where R is as defined above), SO_2Ar where Ar is any aromatic ring system, SOPh, Cl, Br, I, N_3, NR_3+ where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH_2, a nucleophile X, wherein X may be OR9, NR10R11, SR12, SiR13R14R15, SeR16 and wherein each of R9,R10,R11,R12,R13,R14, R15 and R16 is the same or different and may be hydrogen, C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P;

with the proviso that more than two of R5, R5', R6, R6', R7, R7',R8 and R8' is fluorine.

70. The compound as claimed in claim 69 wherein R5, R6, R7 and R8 are the same and are H or F, and R5', R6', R7' and R8' are the same and are different than R5, R6, R7 and R8.

71. The compound as claimed in claim 69 wherein R2 and R2' are the same or different and are hydrogen or C_1-C_6 aliphatic, linear or branched, and R5, R5', R6, R6', R7, R7', R8 and R8' are each fluorine.

72. The compound as claimed in claim 69 wherein R2 and R2' are the same or different and are hydrogen or C_1-C_6 aliphatic, linear or branched, and R5, R5', R6, R6', R8 and R8' are each fluorine, and R7 and R7' are the same or different and are a nucleophile X as claimed in claim 69.

73. The compound as claimed in claim 69 wherein R2 and R2' are the same or different and are hydrogen or C_1-C_6 aliphatic, linear or branched, and R5, R5', R8 and R8' are each fluorine, and R6, R6', R7, R7' are the same or different and are a nucleophile X as claimed in claim 69.

74. The compound as claimed in claim 72 wherein the nucleophile X is hydroxy or C_1-C_6 alkoxy.

75. A modified asymmetric polyfluorinated binaphthyl based ligand wherein the fluorine atom in at least one of positions 5 and 5', 6 and 6', 7 and 7', and 8 and 8' is selectively displaced with a nucleophile.

76. The modified polyfluorinated binaphthyl based ligand as claimed in claim 75 wherein the fluorine atoms at positions 7 and 7′ are selectively displaced with a nucleophile.

77. The modified polyfluorinated binaphthyl based ligand as claimed in claim 75 wherein the fluorine atoms at positions 6, 6′, 7 and 7′ are selectively displaced with a nucleophile.

78. The use of a ligand as claimed in claim 60 for an application selected from the group consisting of asymmetric catalysis with main group elements, transition metal and lanthanide metals, asymmetric reagent with main group elements, transition metal and lanthanide metals, polymer supported catalysis, nucleophilic displacement of fluorine atoms to modify characteristics of molecule, incorporation of molecule into crown ethers for development of phase transfer catalysts, use of compound as a monomer for polymerization, asymmetric polymer supported electrochemical oxidation catalysis, as a chiral auxiliary in a n asymmetric reaction, as a resolving agent for chiral compounds, including but not limited to amines, asymmetric catalysis (reagent) in fluorous phase reactions, as a chiral stationary phase for HPLC and other chromatographic techniques, and phase transfer catalyst between organic, fluorous phase and alkali solutions.

79. An asymmetric ligand comprising an aromatic ring system that is polyfluorinated, that is modified by selectively nucleophilically substituting at least one fluorine atom with a nucleophile.

80. A ligand as claimed in claim 79 wherein the aromatic ring system comprises a biphenyl, binaphthyl, bipyridyl ring system or a derivative thereof.

81. A ligand as claimed in claim 80 wherein the aromatic ring system comprises a binaphthyl ring system or a derivative thereof.

82. A ligand as claimed in claim 79 comprising a nucleophile X, wherein X has the meaning defined in claim 69.

83. A ligand as claimed in claim 82 comprising a nucleophile wherein the nucleophile is hydroxy or C_1-C_6 alkoxy.

84. A ligand as claimed in claim 81 wherein a nucleophile is selectively substituted in at least one of positions 7,7' and 6,6'.

85. A ligand as claimed in claim 84 wherein the nucleophile is substituted in both the 7,7' and 6,6' positions and the nucleophile that is substituted in the 7,7' positions is the same or different than the nucleophile substituted in the 6,6' positions.

86. A ligand as claimed in claim 84 wherein the binaphthyl ring system is a 2, 2' di substituted binaphthyl ring system, and wherein the substituents at the 2 and 2' positions are the same or different and are each OR where R is as defined in claim 64.

87. A ligand as claimed in claim 86 comprising a nucleophile wherein the nucleophile is hydroxy or C_1-C_6 branched or straight chain alkoxy.

88. A ligand as claimed in claim 86 wherein the nucleophile is substituted in both the 7, 7' and 6, 6' positions and the nucleophile that is substituted in the 7, 7' positions is the same or different than the nucleophile substituted in the 6,6' positions.

89. A method of generating a library of a predetermined number of asymmetric ligands comprising:

a) providing an asymmetric polyfluorinated aromatic ring system;

b) selective substituting at least one fluorine atom with a nucleophile; and

c) repeating steps a) and b) a predetermined number of times to obtain a predetermined number of ligands.

90. The method as claimed in claim 89 wherein the aromatic ring system is selected from biphenyl, binaphthyl, bipyridine and derivatives thereof.

91. The method as claimed in claim 89 wherein the same aromatic ring system is provided in each step a) and a different nucleophile is selectively substituted for at least one fluorine atom in each step b).

92. The method as claimed in claim 90 wherein the aromatic ring system is a binaphthyl derivative.

93. The method as claimed in claim 89 wherein the nucleophiles selectively substituted in steps b) are selected from the group of nucleophiles X, wherein X is as defined in claim 69.

94. The method as claimed in claim 93 wherein the nucleophiles selectively substituted in steps b) are selected from hydroxy, and C_1-C_6 alkoxy.

95. The method as claimed in claim 91 wherein in each step b) the nucleophile is selectively substituted in the same position on the aromatic ring system.

96. The method as claimed in claim 91 wherein in each step b) the nucleophile is optionally selectively substituted in different positions.

97. The use of a library of ligands made by a method as claimed in claim 89 to screen the pharmacological activity of each ligand within the library.

98. A compound as claimed in claim 69 wherein R5, R6, R7 and R8 are the same and are H or F, and R5', R6', R7' and R8' are the same and are H or F, and R5', R6', R7' and R8' are different than R5, R6, R7 and R8.

99. The compound as claimed in claim 73 wherein the nucleophile X is hydroxy or C_1-C_6 alkoxy.

IN THE DRAWINGS

Kindly replace the original Figure 8 with the amended Figure 8 submitted herewith.

REMARKS

1) Remarks concerning Amendments to the claims

Claims 60-99 are pending the application. The claims have been amended in view of proceedings at the international level. Independent claims 60, 69, 75, 79 and 89 read as claims 1, 13, 19, 25, and 41 respectively, of the claims as they stood at the completion of international proceedings.

2) Remarks concerning Amendments to the Figures

In the original Figure 8 as filed, substitution is shown at the 5, 5', 7 and 7' positions, as opposed to what was obviously intended from the application, where substitution is at the 6, 6', 7 and 7' positions. Support for this amendment can be found on page 6, lines 22-23, which states:

"Figure 8 is a schematic showing the chemistry of the nucleophilic modification at the 6 and 6' positions."

Further support can be found on page 11, line 28 to page 12, line 8.

It is obvious from the description as filed that the applicant intended to show substitution at the 6, 6', 7 and 7' positions. By the present amendment, the Applicant seeks to correct this obvious error in Figure 8.

In accordance with 37 C.F.R. 1.121(d), two versions of Figure 8 are enclosed, one having the proposed changes are shown in red.

No new matter has been added by the present amendments to the claims or drawings.

Should any Patent Office Official want to telephone, the call should be made to Brian Gray (Registration No. 30017) at (416) 863-3256.

Yours very truly,

Friday 18 January, 2002
Date

Brian Gray
Registration No. 30017

BLAKE, CASSELS & GRAYDON LLP
Box 25, Commerce Court West
Toronto, Ontario
M5L 1A9
Canada

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning at line 4, on page 1 has been amended as follows:

--This application is submitted under 35 U.S.C. 371 from PCT/CA 00/00850 filed July 21, 2000 designating the United States, and claims priority from United States Provisional Patent Application Nos. 60/144, 812 and 60/201,730, filed July 21, 1999 and May 4, 2000, respectively, the specifications of which are hereby incorporated by reference in their entirety. --

Figure 8

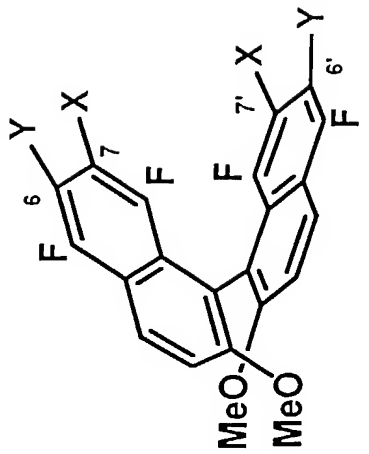
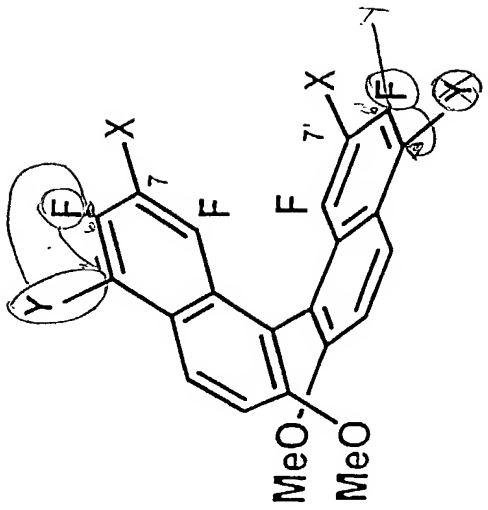


Figure 8



Title: Asymmetric Ligands Having Use As Catalysts

RELATED APPLICATION DATA

This application claims priority from United States Provisional Patent Application Nos. 60/144,812 and 60/201,730, filed July 21, 1999 and May 4, 2000, respectively, the specifications of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to electronically perturbed asymmetric aromatic ligands. In one aspect it relates to polyfluorinated aromatic ligand catalysts that may be nucleophilically modifed. The ligands may be used in catalytic processes.

BACKGROUND OF THE INVENTION

Modern asymmetric synthesis often calls for catalytic transformations. Understanding the balance of steric and electronic factors is required in order to fine-tune a catalyst to achieve optimal rate and selectivity in a particular reaction. The analysis of steric environments around metal centers has traditionally dominated attempts to explain and predict the outcome of metal-based enantioselective processes. In comparison, the importance of electronic effects in asymmetric induction was appreciated only in recent years. Several known catalytic systems employ electronically diverse substituents on ligands in order to modulate reactivity of the metal center.

For example, in the catalytic asymmetric epoxidation of unfunctionalized olefins, electronic properties of substituents on chiral *salen* ligands determine the nature of transition state (M. Palucki et al *J. Am. Chem Soc.* 1998, 120, 948). The later transition state leads to higher enantioselectivities and electronic attenuation of electrophilic Mn=O

centers affords higher levels of enantiomeric excess. Enhancement of enantioselectivity through incorporation of fluorine atoms on chiral phosphine ligands in the asymmetric hydrocyanation of olefins was documented (T.V. Rajanbabu, A.L. Casalnuovo *J. Am. Chem. Soc.* 1996, 118, 6325). The concept of induced electronic asymmetry allows one to increase the enantioselectivity of rhodium-catalyzed hydroboration of olefins (A. Schnyder et al. *Angew Chem. Int. Ed. Engl.* 1995, 34, 931).

Much research has been devoted to the development of chiral ligands. Among these, the 2,2'-dihydroxy-1,1'-binaphthyl ("BINOL") and related molecules with axial chirality have found wide utility in asymmetric catalysis. Over the years, several modifications to the BINOL skeleton aimed at modifying its steric and electronic properties have been reported. For example, partially hydrogenated BINOL was used as a catalyst precursor in enanatioselective alkylation of aldehydes (A.S.C. Chan et al. *J. Am. Chem. Soc.* 1997, 119, 4080), conjugate addition of diethylzinc to cyclic enones (F. Y. Zhang, A.S.C. Chan *Tetrahedron: Asymmetry* 1998, 9, 1179), and ring opening of epoxides (T. Iida et al. *Angew. Chem. Int. Ed. Engl.* 1998, 37, 2223). Incorporation of bromines into the 6 and 6' positions of BINOL, rather remote from the catalytic site, was shown to increase the enantioselectivity of the corresponding titanium catalysts in glyoxolate-ene reactions (M. Terada et al. *Tetrahedron Lett.* 1994, 35, 1994). Bulky triarylsilyl groups at the 3 and 3' positions of BINOL led to increased levels of enantiofacial discrimination of prochiral aldehydes in asymmetric Diels-Alder reactions (Pu; L *Chem. Rev.* 1998, *98*, 2405). 3,3'-dinitrooctahydrobinaphthol was applied in titanium-catalyzed asymmetric oxidation of methyl-p-tolylsulfide (Reetz, M. T. et al. *Tetrahedron Lett.* 1997, *38*, 5273).

SUMMARY OF THE INVENTION

The present invention relates to new asymmetric aromatic ligands that may be used as catalysts. The ligand may be any aromatic ring system

containing one or more electronegative substituents. Preferably, the electronegative substituents are fluorine and the aromatic ring system is axially chiral, such as a biphenyl, binaphthyl or bipyridine derivative. In one preferred embodiment, the aromatic ring system is a binaphthyl derivative.

Fluorine substitution of aromatic groups modifies their properties including configurational stability and catalytic activity. One issue is the nature of steric and electronic effects of fluorination on aromatic based catalysts. The basic premise is that alteration of stabilizing stacking and edge-face interactions significantly affects approach of certain substrates to catalytic reaction centers. Due to fluorine's high electronegativity, electron density in fluoronaphthyl rings is locoated at the periphery, rather than in the ring's centre. The present invention will be illustrated by examples such as preparation of enantiomerically pure fluorobinaphthyl ligands and their application in catalytic asymmetric processes.

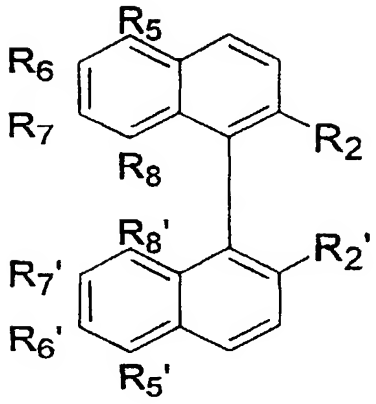
In one aspect of the present invention, there is provided an asymmetric ligand comprising an aromatic ring system substituted with at least one electronegative radical.

In another aspect, there is provided a method of producing a fluorinated asymmetric ligand having an aromatic ring system comprising fluorinating the aromatic ring sytem.

In yet another aspect, the present invention relates to asymmetric ligands comprising an aromatic ring system substituted with at least one electronegative substituent that is modified through nucleophilic substitution. Preferably, the electronegative substituent is fluorine, and the modification consists of displacing fluorine atoms on a polyfluorinated aromatic ring system with a nucleophile. As one example, the fluorine atoms at the 7 and 7' positions of 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1-1'-binaphthyl (F_8BINOL) are selectively displaced with a nucleophile.

Accordingly, the present invention also provides a compound having the Formula III:

Formula III



wherein R2 and R2′ are the same or different and are OR where R may be hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; PR′R″ where R′ and R″ are the same or different and are hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; phosphine oxide; NR‴R⁗ where R‴ and R⁗ are the same or different and are hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; SR⁗⁗R⁗⁗ where R⁗⁗ and R⁗⁗⁗ are the same or different and are hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; and R5, R5′, R6, R6′, R7, R7′, R8 and R8′ are independently hydrogen, fluorine, CN, NO_2, OR (where R is as defined above), SO_2Ar where Ar is any aromatic ring system, SOPh, Cl, Br, I, N_3, NR_3^+ where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH_2, a

nucleophile X, wherein X may be OR9, NR10R11, SR12, SiR13R14R15, SeR16 and wherein each of R9, R10, R11, R12, R13, R14, R15 and R16 may be the same or different and may be hydrogen, C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; with the proviso that at least one of R5 and R5', R6 and R6', R7 and R7', and R8 and R8' is electronegative.

In one preferred embodiment, R5, R6, R7 and R8 are the same and are H or F, and R5', R6', R7' and R8' are the same and are H or F, with the proviso that R5, R6, R7 and R8 are not the same as R5', R6', R7' and R8'.

In another embodiment, R5, R5', R6, R6', R7, R7', R8 and R8' are all the same and are F.

More preferably, each of R, R', R'', R''', R'''', R''''', and R''''''' are H, or C_1-C_6 aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S or P; R7 and R7' are the same and are a nucleophile X, and R5, R5', R6, R6', R8 and R8' are the same and are F .

In still another aspect of the present invention, there is provided a method of generating a library of a predetermined number of asymmetric ligands comprising:

a) Providing an aromatic ring system having at least one electronegative substituent;
b) Selective substituting at least one electronegative substituent with a nucleophile; and
c) Repeating steps a) and b) a predetermined number of times to obtain a predetermined number of ligands.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and

modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be better understood when the following description is read in connection with the accompanying drawings, in which:

Figure 1 shows the preparation of a modified polyfluorinated catalyst;

Figure 2 shows the configurational integrity of the polyfluorobinaphthyl core during nucleophilic modification;

Figure 3 is a schematic diagram showing the chemistry at the 7 and 7' positions of the modified catalyst;

Figure 4 shows the attachment of a modified catalyst to an electrode surface;

Figure 5 shows experimentally observed cyclic voltammogram for the modified electrode surface;

Figure 6 shows the attachment of a modified catalyst to a solid surface;

Figure 7 shows the nucleophilic substitution at the 6, 6' positions of the modified catalyst;

Figure 8 is a schematic showing the chemistry of the nucleophilic modification at the 6 and 6' positions;

Figure 9 illustrates internal nucleophilic displacement in monoprotected F8BINOL; and

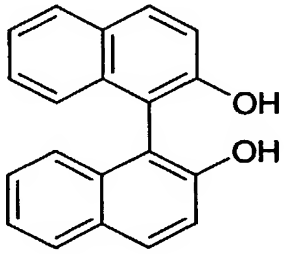
Figure 10 illustrates a synthesis scheme for preparing H_4F_4 ligands.

DESCRIPTION OF THE PREFERRED EMBODIMENT

As previously mentioned, the present invention relates to aromatic asymmetric ligands containing at least one electronegative substituent. Optionally, the ligands may be modified with a nucleophile.

The present invention will be exemplified, by way of example by disclosing the design a new family of polyfluoroaryl ligands that originate from 2,2'-dihydroxy-1,1'-binaphthyl ("BINOL"), a catalyst precursor of broad utility in asymmetric catalysis (R. Noyori *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, 1994). The structure of BINOL is shown in Formula I:

Formula I



While the present invention will be described herein in relation to BINOL derivatives, it will be readily appreciated by those skilled in the art that other compounds having similar structures and properties may be substituted for BINOL. In particular, any aromatic ring structure is suitable for use in connection with the invention. For example, benzene, pyridine, naphthalene, anthracene and their derivatives are suitable for use with the invention (e.g. polyfluorinated benzene and polyfluorinated naphthalene). More preferably, the aromatic ring is one that exhibits axial chirality due to steric hinderance, i.e. the rings are not free to rotate about an axis because of steric hinderance. Such ring systems are known to those skilled in the art, and include biphenyl, binaphthyl, bipyridine and their derivatives.

More preferably, the aromatic ring structure is binaphthyl or a derivative thereof. Most preferably, the aromatic ring structure is a 2, 2' di-substituted binaphthyl derivative, where the substituent is hydroxy, C_1-C_6 alkoxy, phenoxy, phosphino, phosphine oxide, primary or secondary

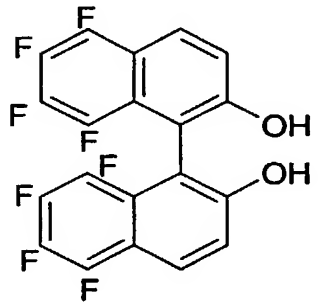
C_1-C_6 amine, or primary or secondary sulfides. Some specific examples of such ring structures include the 2, 2′ dihydroxy, 2, 2′ dimethoxy, 2, 2′ diphosphine, 2, 2′ diphosphine oxide, and 2, 2′ diamino derivatives of binaphthyl. Further, while it may be desirable, it is not necessary that the substituents at the 2 and 2′ positions be the same. For example, the aromatic ring may be a 2-hydroxy, 2′-amino derivative or the like.

Furthermore, while the present invention is described generally in relation to being an aromatic ring substituted with fluorine, it will be appreciated that any relatively small electronegative radical may be utilized. Electronegative radicals are well known to those skilled in the art and include radicals such as CN and NO_2, OR where R is as defined above, SO_2Ar where Ar is any aromatic ring system, SOPh, Cl, Br, I, N_3, NR_3^+ where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, and NH_2, that may be utilized in accordance with the present invention. Preferable electronegative substituents include F, Cl, Br, I, CN, and NO_2. Fluorine is particularly useful in accordance with the present invention, since it is highly electronegative, and does not significantly affect the torsion angle of the aromatic moiety.

Without being limited by theory, the inventors postulate that since the van der Waals radius of fluorine atoms is about 0.27Å larger than that of hydrogen atoms (B.E. Smart *Organofluorine Compounds: Principles and Commerical Applications*, R.E. Banks, ed., Chapter 3, Plenum Press: New York, 1994), the replacement of hydrogens for fluorines at the 5, 5', 6, 6', 7, 7', 8, and 8' positions of BINOL may affect the torsion angle minimally in the resulting 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl ("F_8BINOL", Formula II below). More importantly, considerable electronic perturbations take place due to the net effect of eight fluorine atoms. The electron-deficient nature of the aromatic rings in Formula II should result in a higher oxidative stability compared to Formula I and increased acidity of the hydroxyl groups which could

potentially affect binding to metals and the corresponding substrates in the F_8BINOL-mediated reactions. The increased acidity of the hydroxyl could also result in an increase in the lewis acidity of the bound metal compared to a non fluorinated binol analogue.

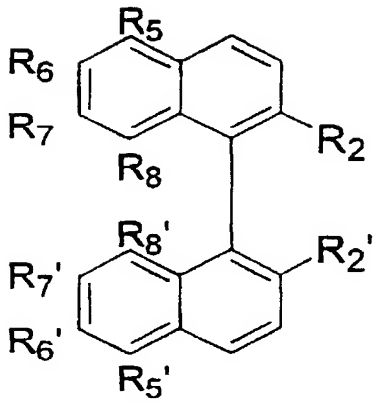
Formula II



Optionally, one or more of the electronegative radicals may be selectively substituted with a nucleophile. More preferably, one or more fluorine atoms on the aromatic ring system are selectively displaced with a nucleophile on a polyfluorinated catalyst such as the catalyst 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (F_8BINOL). Ligands suitable for use as nucleophiles are well known to those skilled in the art and generally include radicals such as alcohols, amines, thiols and phenols. Some examples of suitable nucleophiles include $NH2^-$, PH_3C^-, $PhNH^-$, ArS^-, RO^-, R_2NH, ArO^-, OH^-, $ArNH_2$, NH_3, halogen, where, in each case, Ar is aromatic, and R may be the same or different and is C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P.

The present invention also relates to compounds of the Formula III:

Formula III



wherein R2 and R2′ are the same or different and are OR where R may be hydrogen, C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; PR′R″ where R′ and R″ are the same or different and are hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; phosphine oxide; NR‴R⁗ where R‴ and R⁗ are the same or different and are hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; SR⁗⁗⁗⁗⁗ where R⁗⁗ and R⁗⁗⁗⁗⁗ are the same or different and are hydrogen, or C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; and R5, R5′, R6, R6′, R7, R7′, R8 and R8′ are independently hydrogen, fluorine, CN, NO_2, , OR (where R is as defined above), SO_2Ar where Ar is any aromatic ring system, SOPh, Cl, Br, I, N_3, NR_3^+ where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH_2, a

each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH_2, a nucleophile X, wherein X may be OR9, NR10R11, SR12, SiR13R14R15, SeR16 wherein each of R9, R10, R11, R12, R13, R14, R15, and R16 may be the same or different and may be hydrogen, C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; with the proviso that at least one of R5 and R5', R6 and R6', R7 and R7', and R8 and R8' is electronegative.

In one preferred embodiment, R5, R6, R7 and R8 are the same and are H or F, and R5', R6', R7' and R8' are the same and are H or F, with the proviso that R5, R6, R7 and R8 are not the same as R5', R6', R7' and R8'.

In another embodiment, R5, R5', R6, R6', R7, R7', R8 and R8' are all the same and are F.

In a preferred embodiment, R5, R5', R6, R6', R8 and R8' are fluorine atoms; R7 and R7' are the same, and are a nucleophile X. In another preferred embodiment, R5, R5', R8 and R8' are fluorine atoms, R6 and R6' are the same and are a nucleophile X, and R7 and R7' are the same and are a nucleophile Y where Y has the same definition as X and where X and Y may be the same or different.

Preferably, the nucleophiles X and Y are an OR group, where R is as defined above, and the modified catalyst is prepared from the bis (methylether) or bis(benzyl ether) of F_8BINOL (i.e. where R2 and R2' are methoxy, or benzyloxy) according to the reaction scheme shown in Figure 1.

More preferably, the nucleophiles X and Y are a methoxy or ethoxy group. It will be understood by those skilled in the art that different catalytic applications will have different preferred substiutents.

While the foregoing describes nucleophilic substitution of F_8BINOL at the 7 and 7' positions, it will be readily appreciated by those skilled in the art that the fluorine atoms at other positions may be additionally or alternately substituted. For example, Figure 7 shows the

selective displacement of fluorine atoms at positions 6 and 6' with the nucleophiles X and Y in a modified F_8BINOL containing the ligand A, B or C (where A, B, and C may independently be as previously defined for X) groups at positions 7 and 7'. Figure 8 shows the stereochemistry of a modified F_8BINOL containing nucleophiles at the 6, 6', 7 and 7' positions. In this manner, a matrix of different catalysts may be prepared. Such a matrix is useful in determining what combination of substitutions is most useful for any particular catalytic application.

Selective substitution of the fluorine groups at the 7 and 7' positions with the methoxy group takes place in 95% yield with remarkable selectivity. The configuration integrity of the polyfluorobinaphthyl core during the methoxylation process is shown in Figure 2.

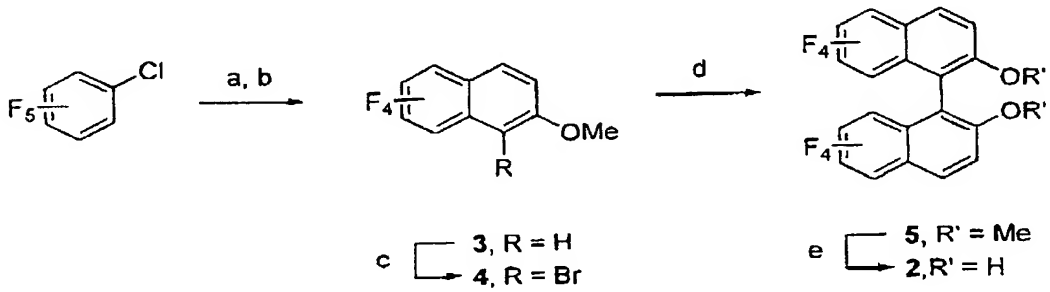
Figure 3 is a schematic diagram showing the chemistry of the modified catalyst at the 7 and 7' positions. The favourable conformation of the modified catalyst leads to many improved properties and utilities for the catalyst. For example, facile modification at the 7,7' positions suggests the possibility of placing the catalytic reaction center in that area. Direct connection of heteroatoms by nucleophilic substitution should lead to novel C2 symmetrical ligands. Their monodentate nature will result from the steric constrains that should defeat chelation. In order to create different bidentate sites at the 7 and 7' positions, linkers of varied lengths may be attached to the 7 and 7' positions. Examples of linkers and their methods of attachment are well known in the art. Examples of linkers include $-OCH_2CH_2NH_2$, $-OCH_2CH_2OH$, $-OCH_2NH_2$, $-OCH_2PH_2$, $-CH_2CH_2SH$, etc.

It will be appreciated by those skilled in the art that the compounds of the present invention may be in racemic or optically pure form. In a preferred embodiment, the compounds are in the optically pure S form.

The examples following particularize the preparation of compounds within the scope of the present invention. Generally

speaking, unsubstituted polyfluorinated compounds may be prepared according to Scheme 1. While reference is made to fluorinated aromatics, it will be appreciated that similar standard processes may be used for other compounds within the scope of the present invention.

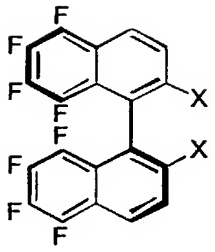
Scheme 1[a]



[a]Key. (a) *n*-BuLi, ether, -78 °C; (b) 3-methoxythiophene, -78 °C to r.t.; (c) NBS, acetonitrile, r.t.; (d) Cu°, 175 °C; (e) BBr_3, dichloromethane, r.t.

Nucleophilic displacement of aromatic fluorine is a well known reaction with a wide scope and utility [Welch, 2000 #14]. The presence of the fluorine atoms in the 2,2′ dihydroxy BINOL derivative (compound 1a in Formula IV) suggests nucleophilic substitution as a potential route to ligand modification. Standard methoxylation with NaOMe of 5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl (compound 1b in Formula IV) results in nucleophilic substitution of fluorine, but a complicated mixture of poly(methoxylated) products is obtained, indicating lack of regioselectivity. However, the presence of the methoxy substituents at the 2 and 2' positions in the bis(methyl) ether (compound 1c in Formula IV) is sufficient to secure high regioselectiveity of the methoxylation reaction. Double substitution proceeds smoothly and results in the 7,7′-bis(methoxy) product in good chemical yield and with high regioselectivity.

Formula IV

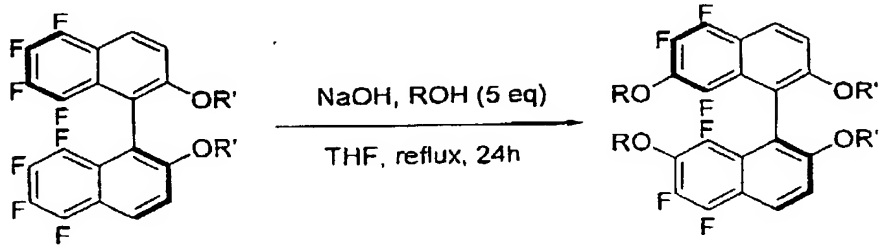


1a, X = OH
1b, X = H
1c, X = OMe
1d, X = OBn

Other alkoxy nucleophiles behave in a similar manner and may be similarly substituted (See Scheme 2 below). However, subsequent dealkylation with boron tribromide suffers from poor chemoselectivity. Therefore, the use of the bis(benzyl) ether (compound 1d in Formula IV) or another selective protective group which benefits from selective deprotection via hydrogenation, is preferable in order to arrive at the final bis-2,2'-hydroxy stage.

No racemization is observed when enantiomerically pure bis(methoxy) derivative (compound 1c in Formula IV) is used in the methoxylation reaction.

Scheme 2



R	R'	yield (%)
Me	Me	95
Et	Bn	88
*i*Pr	Bn	88
*t*Bu	Bn	88

It will, of course, be appreciated that the nucleophilical substitution process may be utilized with not only the binaphthyl derivatives above described, but with any of the aromatic ring systems previously described. For example, the selective substitution may be be used on polyfluorinated benzene or polyfluorinated naphthalene systems, or indeed any aromatic ring system having at least one electronegative radical.

Those skilled in the art will understand that the compounds of the present invention have many useful applications. Such applications include asymmetric catalysis with main group elements, transition metal and lanthanide metals; asymmetric reagent with main group elements, transition metal and lanthanide metals; polymer supported catalysis; incorporation of molecules into crown ethers for development of phase transfer catalysts; use of compounds as a monomer for polymerization; asymmetric polymer supported electrochemical oxidation catalysis; as a chiral auxiliary in an asymmetric reaction; as a resolving agent for chiral compounds, including but not limited to amines; asymmetric catalysis (reagent) in fluorous phase reactions; as a chiral stationary phase for HPLC and other chromatographic techniques; phase transfer catalyst between organic, fluorous phase and alkali solutions.

One specific application is to develop combinatorial approaches to catalyst development. It is possible to determine which substitution pattern on the F_8BINOL moiety gives optimal catalyst with regard to rate and selectivity in a particular reaction. To address this issue, the dihedral angle and electron distribution in F_8BINOL may be varied by replacing fluorine atoms at the 7,7' positions with a variety of nucleophiles to develop analogs of F_8BINOL.

It is also possible to generate libraries of such analogs using solution and solid-phase parallel synthesis. The structure/activity relationships may be deciphered based on screening the resulting catalyst libraries in a variety of reactions including hetero Diels-Alder, aziridination, direct aldol, and imine hydrogenation processes.

A library of compounds may also be generated for any other suitable purpose. For example, it is possible to build a library of compounds for pharmaceutical testing. With the highly selective substitution, it is possible to start with a base compound and develop a number of related but different compounds by selectively substituting different nucleophiles at the same or different locations on the base compound. Pharmacological activity screening may then be done on the library of compounds to determine which compounds have the highest activity.

The highly selective nucleophilic functionalization of the F_8BINOL core will allow the attachment of the modified catalysts to an electrode surface or a solid support. Figure 4 shows the attachment of the modified catalyst to an electrode surface and Figure 5 shows experimentally observed cyclic voltammogram for the modified electrode surface.

Figure 6 shows the attachment of the modified catalyst to a solid support. In particular, Figure 6 exemplifies an approach toward libraries of TentaGel S OH resin-linked catalysts. An alternative to this strategy is to introduce functionality X directly onto the ligand-derivatized resin. On bead screening for the catalytic activity will allow the fine-tuning of the ligand's torsion angle using solid-phase chemistry by manipulating the 7,7' substituents. It should be emphasized that established routes to modified BINOL involve rather harsh electrophilic functionalization which puts substituents into the 6,6' positions and necessitates a subsequent resolution step which is not feasible under combinatorial protocols commonly performed on a microgram scale. On the contrary, high configurational stability of F_8BINOL under basic conditions will enable the use the homochiral starting material without the loss of enantiomeric purity during the nucleophilic substitution. As well, substituents at the 7,7' positions could have direct steric influence over the dihedral angle which should modulate the catalytic activity, a feature not available for the 6,6' substitution pattern.

Figure 9 shows internal nucleophilic displacement in monoprotected F_8BINOL which illustrates that the axial chirality of F_8BINOL provides convenient access to ligands with helical chirality.

Utility of the poly(alkoxylated) ligands in asymmetric catalysis was illustrated using diethylzinc addition to aldehydes. We observed high levels of enantioselectivity in titanium-catalyzed addition of diethylzinc to aldehydes using x and x under the conditions where the formation of the monomeric catalysts of 1:1 composition is favored.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

The following examples, which are non-limiting, are illustrative of the present invention. The scope of the invention is limited only by the claims.

EXAMPLES

I. FLUORINE SUBSTITUTION OF BINOL

(a) 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl

Racemic form of the compound 5,5',6,6',7,7',8,8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl (compound 2 in Scheme 1) was prepared according to Scheme 1 above. Tetrafluorobenzyne, formed by treating commercially available chloropentafluorobenzene with *n*-butyllithium at -78°C, was reacted with 3-methoxythiophene, obtained from 3-bromothiophene using a literature procedure (methoxythiophene preparation). Upon the *in situ* extrusion of sulfur, 2-methoxy-5,6,7,8-tetrafluoronaphthalene (Formula III) was obtained in 52% yield. 5,6,7,8-Tetrafluoro-2-naphthol, prepared from 2-methoxy-5,6,7,8-tetrafluoronaphthalene by demethylation with BBr_3, did not undergo the $FeCl_3$- catalyzed oxidative coupling, commonly used for the preparation of BINOL from 2-naphthol (BINOL prep via $FeCl_3$ coupling). Instead,

substitution of hydrogen for chlorine at the 1 position of the aromatic ring took place. Higher oxidation potential of 5,6,7,8-tetrafluoro-2-naphthol (2.07V *vs* Ag/AgCl compared to 1.47V *vs* Ag/AgCl for BINOL) is a likely reason for the lack of reactivity in the oxidative coupling.

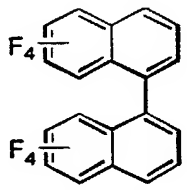
Therefore, the reductive route through intermediacy of the 1-brominated derivative (compound 4 in Scheme 1), prepared in 52% yield from compound 3 in Scheme 1 by treatment with *N*-bromosuccinimide in acetonitrile, was utilized. The Ullmann homocoupling of the 1-bromo derivative, facilitated by the presence of aromatic fluorines, gave the desired bis(methoxy) product (compound 5 in Scheme 1) in 85% yield. Demethylation of the bis(methoxy) derivative with BBr_3 furnished F_8BINOL (compound 2 in Scheme 1) in 88% yield. Finally, recrystallization from methanol/water gave pure F_8BINOL as white needles. After several unsuccessful attempts at resolving F_8BINOL, the diastereomeric bis(menthyl)carbonates were chromatographically separated by reacting racemic F_8BINOL with excess (-)-menthylchloroformate. Treatment of each diastereomer with dilute NaOH followed by extraction with diethyl ether afforded (-)-F_8BINOL and (+)-F_8BINOL, respectively. The enantiomeric excess, determined using chiral HPLC (Chiralpak AD column), was found to be >99.9% in each case.

(b) 5,6,7,8-tetrafluoro-1-naphthol

Replacement of aromatic hydrogens for fluorines is known to substantially increase barriers to axial torsion in substituted biphenyls. For example, fluorination of the 4 and 5 positions of 9,10-dihydrophenanthrene raises the torsion barrier from 4.1 to 10.3 kcal/mol (M. Schlosser, D. Michel *Tetrahedron* 1996, *52*, 99 and references cited therein). In order to estimate the effect of polyfluorination on atropisomerism in the octafluoro-1,1'-binaphthyl species racemic 5,6,7,8-octafluoro-1,1'-binaphthyl (compound 6 below) was prepared and its X-ray structure determined. Racemic 5,6,7,8-octafluoro-1,1'-binaphthyl was

prepared from 5,6,7,8-tetrafluoro-1-naphthol (G. W. Gribble, C. G. LeHoullier, M. P. Sibi, R. W. Allen *J. Org. Chem.* 1985, *50*, 1611) by Ni(0)-catalyzed homocoupling of its trifluoromethanesulfonate ester in NMP at 100 °C. The torsion angles in the molecular structures of BINOL and F_8BINOL were not compared due to the possibility of intramolecular OH-F hydrogen bonding in the crystal lattice that could have complicated direct comparison of geometric parameters. Remarkably, the torsion angle between the two tetrafluorinated naphthyl planes in 5,6,7,8-octafluoro-1,1'-binaphthyl is only 0.7° larger than in the parent hydrido derivative (70.2° for octafluoro-1,1'-binaphthyl *vs* 69.5° for 1,1'-binaphthyl (R. Kuroda, S. F. Martin J. Chem. Soc. Perkin Trans II 1981, 167)).

To further understand atropisomerism in F_8BINOL acid-promoted racemization of its (-) enantiomer was investigated. This process is known to operate for BINOL. Remarkably, F_8BINOL remains optically active (99.9% e.e) after 24 hours in boiling THF/HCl mixture, whereas BINOL rapidly racemizes under these conditions!



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Polyfluorination of aromatic nuclei is also known to decrease pKa's of bound heteroatoms (B. E. Smart, in: *Organofluorine compounds: Principles and Commercial Applications* (R. E. Banks, ed.), Chapter 3, Plenum Press: New York, 1994). For example, incorporation of four fluorine atoms into the aromatic skeleton of tyrosine results in the pKa' decrease of the ring-bound hydroxyl group by 5 units (K. Kim, P. A. Cole *J.*

Am. Chem. Soc. 1998, *120*, 6851). It was determined that the pKa' of the hydroxyl group in F_8BINOL decreases by 1 unit upon octafluorination (BINOL: pKa' 10.28; F_8BINOL: pKa' 9.29). Another important consequence of fluorination is anodic shift in the oxidation potential of F_8BINOL, which was found to be more positive than that of binaphthyl by 0.6 V, a useful property for applications in oxidation catalysis.

These results lead to the conclusion that the effect of fluorine on the reactivity of F_8BINOL is primarily electronic in nature. The desired conformational flexibility, one of the most important characteristics of BINOL allowing it to coordinate a wide variety of metals, should be preserved. Remarkable configurational stability of either enantiomer of F_8BINOL is perhaps its most valuable property.

II. NUCLEOPHILIC SUBSTITUTION

General: Anhydrous THF was obtained by distillation over sodium benzophenone ketyl under nitrogen. 2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl and 2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl were prepared according to literature procedures. Column chromatography was carried out using 230-400 mesh silica gel.

(a) 2,2',7,7'-tetramethoxy-5,5',6,6',8,8'-hexafluoro-1,1'-binaphthyl(1)

To a solution of 2,2'-dimethoxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl (91.7mg, 0.2mmol) in anhydrous THF (10mL) was added 81µl (2.0mmol) methanol and 112mg (2.0mmol) KOH . The mixture was stirred and refluxed for 12hrs. The reaction mixture was diluted with ether and washed with aqueous HCl (5%) . The result organic extract was dried over $MgSO_4$ and concentrated. Purification of the residue by chromatography over silica afforded pure (1) (91.0mg, 84%) as white solid.

^{1}HNMR(400 MHz, $CDCl_3$): δ8.10(d, J=9.2Hz, 2H), 7.42(d, J=9.2Hz, 2H), 3.91(S, 6H), 3.75(S, 6H). ^{19}FNMR(400MHz, $CDCl_3$): δ -140.93(d, J=16.8Hz), -152.65(dd, J=16.8Hz, 3.2Hz), -158.80(d, J=19.6Hz). ^{13}CNMR(100MHz, $CDCl_3$): δ155.6(s), 147.2(dt, J=249.2Hz, 3.8Hz), 142.4(ddd, J=249.0Hz, 6.1Hz, 4.6Hz), 139.9(ddd, J=250.0Hz, 9.2Hz, 4.5Hz), 135.9(m), 121.6(m), 120.9(m), 117.2(s), 116.0(dd, J=9.9Hz, 4.5Hz), 114.3(s), 62.5(s), 56.9(s). HREI-MS, m/z: Calcd for $C_{24}H_{16}F_6O_4$ 482.0953; found, 482.0958.

(b) 2,2'-dimethoxy-7,7'-diethoxy-5,5'6,6',8,8'-hexafluoro-1,1'-binaphthyl(2)

In accordance to the general procedure described above, but 116μl (2.0mmol) ethanol was used instead of methanol. A total of 78.1mg (77%) of 2 was obtained as white solid.

^{1}HNMR(400MHz, $CDCl_3$): δ 8.09(d, J=9.2Hz, 2H), 7.38(d, J=9.6Hz, 2H), 4.11(q, J=6.8Hz, 4H), 3.73(S, 6H), 1.29(t, J= 6.8Hz, 6H). ^{19}FNMR(400MHz, $CDCl_3$): δ -139.91(d, J=16.8Hz), -152.68(dd, J=16.8Hz, 2.8Hz), -158.08(d, J=19.6Hz). ^{13}CNMR(100MHz, $CDCl_3$):δ155.6(s), 147.6(dt, J=249.3Hz, 3.8Hz), 142.3(ddd, J=247.0Hz, 6.0Hz, 4.6Hz), 140.2(ddd, J=246.0Hz, 9.2Hz, 4.5Hz), 134.8(m), 121.5(m), 120.9(m), 117.2(s), 116.1(dd, J=9.8Hz, 3.8Hz), 114.2(s), 71.0(s), 56.9(s), 15.5(s). HREI-MS, m/z: Calcd for $C_{26}H_{20}F_6O_4$, 510.1255; found, 510.1266.

(c) 2,2'-dimethoxy-7,7'-di-*iso*-propoxy-5,5',6,6',8,8'-hexafluoro-1,1'-binaphthyl(3)

In accordance to the general procedure described above, but 154μl (2.0mmol) *iso*-propanol was used instead of methanol. A total of 87.9mg (89%) of 3 was obtained as white foam.

^{1}HNMR(400MHz, $CDCl_3$): δ8.08(d, J=9.2Hz, 2H), 7.38(d, J=9.2Hz, 2H), 4.36(sep, J=6.0Hz, 2H), 3.71(s, 6H), 1.23(dd, J=6.0Hz, 3.2Hz, 12H).

^{19}FNMR(400MHz, $CDCl_3$): δ -157.19(d, J=19.6Hz), -152.81(dd, J=16.8Hz, 2.8Hz), -138.60(d, J=16.8Hz). ^{13}CNMR(100MHz, $CDCl_3$): δ 155.6(s), 148.2(dt, J=250.0Hz, 3.8Hz), 142.3(ddd, J=247.0Hz, 6.0Hz, 4.6Hz), 140.6(ddd, J=245.0Hz, 9.2Hz, 3.8Hz), 133.8(m), 121.5(m), 120.9(m), 117.3(s), 116.2(dd, J=10.6Hz, 3.8Hz), 114.2(s), 77.7(s), 56.8(s), 22.4(s). HREI-MS m/z: Calcd for $C_{28}H_{24}F_6O_4$ 538.1583; found, 538.1579.

(d) 2,2'-dimethoxy-7,7'-dibenzyloxy-5,5',6,6',8,8'-hexafluoro-1,1'-binaphthyl(4)

In accordance to the general procedure described above, but 207μl (2.0mmol) benzyl alcohol was uesd instead of methanol. A total of 98.6mg(78%) of 4 was obtained as white foam. ^{1}HNMR(400MHz, $CDCl_3$): δ8.07(d, J=9.2Hz, 2H), 7.37-7.22(m, 12H), 5.06(s, 4H), 3.68(s, 6H). ^{19}FNMR(400MHz, $CDCl_3$): δ -138.78(d, J=16.8Hz), -152.49(dd, J=16.8Hz, 2.8Hz), -157.48(d, J=20.8Hz). ^{13}CNMR(100MHz, $CDCl_3$): δ155.6(s), 147.6(dt, J=250.0Hz, 3.8Hz), 142.3(ddd, J=247.0Hz, 6.8Hz, 4.6Hz), 140.1(ddd, J=246.0Hz, 9.1Hz, 3.8Hz), 136.3(s), 134.4(m), 128.7(d, J=3.1HZ), 128.6(d, J=4.6Hz), 128.5(s), 121.6(m), 120.9(m), 117.2(s), 116.2(dd, J=9.8Hz, 4.6Hz), 114.3(s), 76.5(s), 56.9(s). HREI-MS, m/z: Calcd for $C_{36}H_{24}F_6O_4$, 634.1560; found, 634.1579.

(e) 2,2'-dibenzyloxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl(5)

To a solution of 2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octafluoro-1,1'-binaphthyl (215.2mg, 0.5mmol) and potassium carbonate (691mg, 5mmol) in THF(15mL) was added benzyl bromide (0.6mL, 5mmol). The mixture was stirred and refluxed for 20hrs. The reaction mixture was diluted with ether and washed with aqueous HCl (5%). The solvent and excess benzyl bromide were removed under reduced pressure. Recrystallization from a Hexanes and dichloromethane mixture gave white solid (224.2mg, 80%).

^{1}HNMR(400MHz, $CDCl_3$): δ8.16(d, J=9.6Hz, 2H), 7.50(d, J=9.6Hz, 2H), 7.23-7.16(m, 6H), 6.98-6.96(m,4H), 5.12(s, 4H). ^{19}FNMR(300MHz, $CDCl_3$): δ-146.72(t, J=17.7Hz), -150.55(dd, J=16.2Hz, 5.1Hz), -158.68(t, J=20.1Hz), -163.22(t, J=20.1Hz).

(e) 2,2′-dibenzyloxy-7,7′-dimethoxy-5,5′,6,6′,8,8′-hexafluoro-1,1′-binaphthyl(6)

To a solution of 2,2′-dibenzyloxy-5,5′,6,6′,7,7′,8,8′-octafluoro-1,1′-binaphthyl(5) (224.2mg, 0.4mmol) and potassium hydroxide (224mg, 4.0mmol) in THF(20mL) was added methanol (162μl, 4.0mmol). The mixture was stirred and refluxed for 12hrs. The reaction mixture was diluted with ether and washed with aqueous HCl (5%). The result organic extract was dried over $MgSO_4$ and concentrated. Purification of the residue by chromatography over silica afforded pure (6) as white foam (197.9mg, 78%). ^{1}HNMR(400MHz, $CDCl_3$): δ7.93(d, J=9.2Hz, 2H), 7.24(d, J=9.6Hz, 2H), 7.01-6.96(m, 6H), 6.76(d, J=7.2Hz, 4H), 4.90(s, 4H), 3.74(s, 6H). ^{19}FNMR(300MHz, $CDCl_3$): δ-140.18(d, J=17.3Hz), -152.35(dd, J=16.7Hz, 3.1Hz), -158.30(d, J=21.5Hz).

(f)2,2′-dihydroxy-7,7′-dimethoxy-5,5′,6,6′,8,8′-hexafluoro-1,1′-binaphthyl(7)

To a solution of 2,2′-dibenzyloxy-7,7′-dimethoxy-5,5′,6,6′,8,8′-hexafluoro-1,1′-binaphthyl(6) (126.5mg, 0.2mmol) was added Pd/C(85.2mg, 10%) under a hydrogen atmosphere at room temperature. After being stirred at the same temperature for 10hrs, the reaction mixture was filtered and concentrated. Purification of the residue by chromatography over silica afforded pure (7) (quantitatively) as white foam. ^{1}HNMR(400MHz, $CDCl_3$): δ8.06(d, J=8.8Hz, 2H), 7.30(d, J=9.2Hz, 2H), 5.39(s, 2H), 3.92(s, 6H). ^{19}FNMR(400MHz, $CDCl_3$): δ -142.14(d, J=15.2Hz), -

151.24(dd, J=16.8Hz, 2.8Hz), -157.16(d, J=19.6Hz). ^{13}CNMR(100MHz, $CDCl_3$): δ 153.2(s), 146.6(dt, J=248.5Hz, 3.8Hz), 142.7(ddd, J=248.0Hz, 6.0Hz, 4.6Hz), 140.3(ddd, J=248.0Hz, 8.3Hz, 4.6Hz), 136.7(m), 123.5(m), 120.5(m), 118.5(s), 115.9(dd, J=10.6Hz, 3.8Hz), 108.6(s), 62.5(m). HREI-MS: m/z: calcd for $C_{22}H_{12}F_6O_4$ 454.0642; found, 454.0640.

WHAT IS CLAIMED IS:

1. An asymmetric ligand comprising an aromatic ring system substituted with at least one electronegative radical.

2. The ligand as claimed in claim 1 wherein the aromatic ring system comprises benzene, pyridine, naphthalene, anthracene or a derivative thereof.

3. The ligand as claimed in claim 1 wherein the aromatic ring system is axially chiral.

4. The ligand as claimed in claim 3 wherein the aromatic ring system comprises a biphenyl, binaphthyl, bipyridine ring system or a derivative thereof.

5. The ligand as claimed in claim 4 wherein the aromatic ring system comprises a binaphthyl derivative.

6. The ligand as claimed in claim 5 wherein the aromatic ring system comprises a 2, 2′ di substituted binaphthyl ring system.

7. The ligand as claimed in claim 6 wherein the aromatic ring system is a 2, 2′ di substituted binaphthyl ring system, and wherein the substitutents at the 2 and 2′ positions are the same or different, and are each OR where R may be hydrogen, C_1-C_{20} aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P, PR′R″ where R′ and R″ are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P, phosphine oxide, NR‴R⁗ where R‴ and R⁗ are the

same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P, SR''''R'''''' where R'''' and R'''''' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P.

8. The ligand as claimed in claim 7 wherein R is hydrogen, or C_1-C_6 alkyl which is linear or branched.

9. The ligand as claimed in any one of claims 1 to 8 wherein the electronegative radical is fluorine, Cl, Br, I, CN, or NO_2.

10. The ligand as claimed in any one of claims 1 to 8 wherein the electronegative radical is fluorine.

11. The ligand as claimed in any one of claims 1 to 8 wherein the aromatic ring system is polyfluorinated.

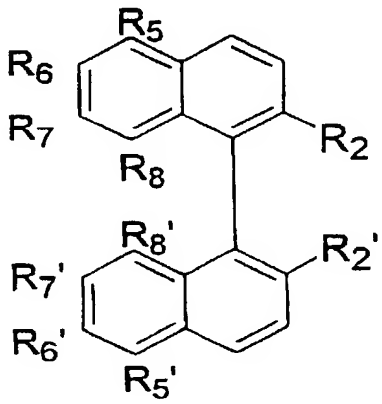
12. The ligand as claimed in claim 6 or 7 wherein the 5, 6, 7, and 8 positions of the binaphthyl ring system are fluorinated and the 5', 6', 7', and 8' positions of the binaphthyl ring system are not substituted with an electronegative radical.

13. The ligand as claimed in claim 6 or 7 wherein the 5, 6, 7, and 8 positions of the binaphthyl ring system are not substituted with an electronegative radical, and the 5', 6', 7', and 8' positions of the binaphthyl ring system are fluorinated.

14. The ligand as claimed in claim 5, 6, 7 or 8 wherein the electronegative radical is fluorine, and the binaphthyl ring system is fluorinated at the 5, 5', 6, 6', 7, 7', 8 and 8' positions.

15. The ligand as claimed in claim 8 which is selected from the group of ligands comprising 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-dihydroxy-1,1'-binaphthyl, 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-dimethoxy-1,1'-binaphthyl, 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-di-n-propoxy-1,1'-binaphthyl and 5, 5', 6, 6', 7, 7', 8, 8'-octafluoro-2,2'-di-i-propoxy-1,1'-binaphthyl.

16. A compound of the formula III:



wherein R2 and R2' are the same or different and are OR where R may be hydrogen, C_1-C_{20} alkyl aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; PR'R'' where R' and R'' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; phosphine oxide; NR'''R'''' where R''' and R'''' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; SR'''''R''''''

where R'''' and R''''' are the same or different and are hydrogen, or C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P; and

R5, R5', R6, R6', R7, R7', R8 and R8' are independently hydrogen, fluorine, CN, or NO_2, OR (where R is as defined above), SO_2Ar where Ar is any aromatic ring system, SOPh, Cl, Br, I, N_3, NR_3^+ where each R is the same or different and may be as defined above, OAr where Ar is as defined above, SR where R is as defined above, NH_2,, a nucleophile X, wherein X may be OR9, NR10R11, SR12, SiR13R14R15, SeR16 and wherein each of R9, R10, R11, R12, R13, R14, R15 and R16 is the same or different and may be hydrogen, C_1-C_{20} that may be aromatic, aliphatic, linear or branched, saturated or unsaturated, unsubstituted or substituted with N, O, S, or P, with the proviso that at least one of R5, R5', R6, R6', R7, R7', R8 and R8' is electronegative.

17. The compound as claimed in claim 16 wherein R5, R6, R7 and R8 are the same and are H or F, and R5', R6', R7' and R8' are the same and are different than R5, R6, R7 and R8.

18. The compound as claimed in claim 16 wherein R2 and R2' are the same or different and are hydrogen or C_1-C_6 aliphatic, linear or branched, and R5, R5', R6, R6', R7, R7', R8 and R8' are each fluorine.

19. The compound as claimed in claim 16 wherein R2 and R2' are the same or different and are hydrogen or C_1-C_6 aliphatic, linear or branched, and R5, R5', R6, R6', R8 and R8' are each fluorine, and R7 and R7' are the same or different and are a nucleophile X as claimed in claim 16.

20. The compound as claimed in claim 16 wherein R2 and R2′ are the same or different and are hydrogen or C_1-C_6 aliphatic, linear or branched, and R5, R5′, R8 and R8′ are each fluorine, and R6, R6′, R7, R7′ are the same or different and are a nucleophile X as claimed in claim 13.

21. The compound as claimed in claim 19 or 20 wherein the nucleophile X is hydroxy or C_1-C_6 alkoxy.

22. A modified polyfluorinated binaphthyl based ligand wherein the fluorine atoms in at least one of positions 5 and 5′, 6 and 6′, 7 and 7′, and 8 and 8′ is selectively displaced with a nucleophile.

23. The modified polyfluorinated binaphthyl based ligand as claimed in claim 22 wherein the fluorine atoms at positions 7 and 7′ are selectively displaced with a nucleophile.

24. The modified polyfluorinated binaphthyl based ligand as claimed in claim 23 wherein the fluorine atoms at positions 6, 6′, 7 and 7′ are selectively displaced with a nucleophile.

25. A ligand as claimed in any one of claims 1 to 24 wherein the ligand is linked to a solid support.

26. A ligand as claimed in any one of claims 1 to 24 wherein the ligand is linked to an electrode surface.

27. The use a ligand as claimed in any one of claims 1 to 26 for an application selected from the group consisting of asymmetric catalysis with main group elements, transition metal and lanthanide metals, asymmetric reagent with main group elements, transition metal and

lanthanide metals, polymer supported catalysis, nucleophilic displacement of fluorine atoms to modify characteristics of molecule, incorporation of molecule into crown ethers for development of phase transfer catalysts, use of compound as a monomer for polymerization, asymmetric polymer supported electrochemical oxidation catalysis, as a chiral auxiliary in an asymmetric reaction, as a resolving agent for chiral compounds, including but not limited to amines, asymmetric catalysis (reagent) in fluorous phase reactions, as a chiral stationary phase for HPLC and other chromatographic techniques, and phase transfer catalyst between organic, fluorous phase and alkali solutions.

28. An asymmetric ligand comprising an aromatic ring system and at least one electronegative substituent, that is modified by selectively nucleophilically substituting at least one electronegative substituent with a nucleophile.

29. A ligand as claimed in claim 28 wherein the aromatic ring system comprises a biphenyl, binaphthyl, bipyridine ring system or a derivative thereof.

30. A ligand as claimed in claim 28 wherein the aromatic ring system is axially chiral.

31. A ligand as claimed in claim 30 wherein the electrophilic substituent comprises fluorine.

32. A ligand as claimed in claim 31 wherein the aromatic ring system comprises a biphenyl, binaphthyl or bipyridine ring system or a derivative thereof.

33. A ligand as claimed in claim 32 wherein the aromatic ring system comprises binaphthyl ring system or a derivative thereof.

34. A ligand as claimed in any one of claims 28 to 33 comprising a nucleophile X, wherein X has the meaning defined in claim 16.

35. A ligand as claimed in any one of claims 28 to 33 comprising a nucleophile wherein the nucleophile is hydroxy or C_1-C_6 alkoxy.

36. A ligand as claimed in claim 33 wherein a nucleophile is selectively substituted in the 7 and 7′ positions.

37. A ligand as claimed in claim 33 wherein a nucleophile is selectively substituted in the 7, 7′, 6 and 6′ positions.

38. A ligand as claimed in claim 37 wherein the nucleophile substituted in the 7 and 7′ positions is the same as the nucleophile substituted in the 6 and 6′ positions.

39. A ligand as claimed in claim 37 wherein the nucleophile substituted in the 7 and 7′ positions is different from the nucleophile substituted in the 6 and 6′ positions.

40. A ligand as claimed in claim 27 wherein the binaphthyl ring system is a 2, 2′ di-substituted binaphthyl ring system, and wherein the substituents at the 2 and 2′ positions are the same or different and are each OR where R is as defined in claim 7.

41. A ligand as claimed in claim 32 comprising a nucleophile X wherein X is as defined in claim 16.

42. A ligand as claimed in claim 40 comprising a nucleophile wherein the nucleophile is hydroxy or C_1-C_6 branched or straight chain alkoxy.

43. A ligand as claimed in claim 40 wherein a nucleophile is selectively substituted in the 7 and 7′ positions on the binaphthyl ring system.

44. A ligand as claimed in claim 40 wherein a nucleophile is selectively substituted in the 6 and 6′ positions on the binaphthyl ring system.

45. A ligand as claimed in claim 44 wherein the same nucleophile is selectively substituted in the 6, 6′, 7 and 7′ positions.

46. A ligand as claimed in claim 44 wherein different nucleophiles are selectively substituted in the 7 and 7′ positions and in the 6 and 6′ positions.

47. A method of generating a library of a predetermined number of asymmetric ligands comprising:
   a) Providing an aromatic ring system having at least one electronegative substituent;
   b) Selective substituting at least one electronegative substituent with a nucleophile; and
   c) Repeating steps a) and b) a predetermined number of times to obtain a predetermined number of ligands.

48. The method as claimed in claim 47 wherein the same aromatic ring system is provided in each step a) and a different nucleophile is selectively substituted for at least one electronegative substituent in each step b).

49. The method as claimed in claim 47 wherein the aromatic ring system provided in step a) is selected from benzene, pyridine, naphthalene, anthracene and their derivatives.

50. The method as claimed in claim 48 wherein the aromatic ring system is axially chiral.

51. The method as claimed in claim 50 wherein the aromatic ring system is selected from biphenyl, binaphthyl, bipyridine and derivatives thereof.

52. The method as claimed in claim 51 wherein the aromatic ring system is a binaphthyl derivative.

53. The method as claimed in 47 wherein the electronegative substituent is selected from the group of electronegative substituent consisting of fluorine, Cl, Br, I, CN and NO_2.

54. The method as claimed in claim 51 or 52 wherein the electronegative substituent is fluorine.

55. The method as claimed in any one of claims 47 to 54 wherein the nucleophiles selectively substituted in steps b) are selected from the group of nucleophiles X, wherein X is as defined in claim 16.

56. The method as claimed in any one of claims 47 to 54 wherein the nucleophiles selectively substituted in steps b) are selected from hydroxy, and C_1-C_6 alkoxy.

57. The method as claimed in claim 48 wherein in each step b) the nucleophile is selectively substituted in the same position on the aromatic ring system.

58. The method as claimed in claim 48 wherein in each step b) the nucleophile is optionally selectively substituted in different positions.

59. The use of a library of ligands made by a method as claimed in any one of claims 47 to 58 to screen the pharmacological activity of each ligand within the library.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07386 A2

(51) International Patent Classification[7]: C07C 39/38, 43/225, 43/23, C07B 53/00

(21) International Application Number: PCT/CA00/00850

(22) International Filing Date: 21 July 2000 (21.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/144,812 21 July 1999 (21.07.1999) US
60/201,730 4 May 2000 (04.05.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

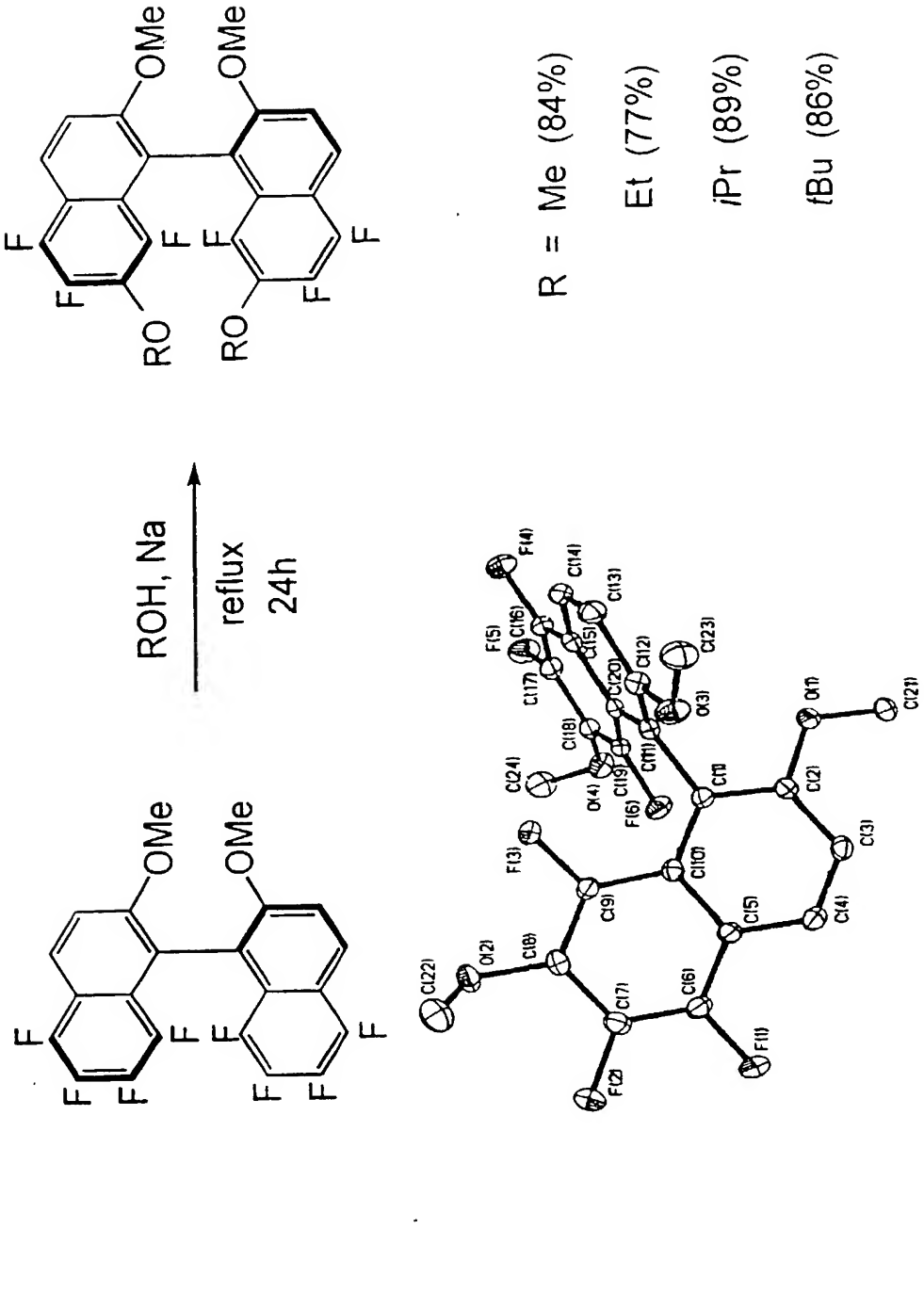
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/07386 A2

(54) Title: ASYMMETRIC LIGANDS HAVING USE AS CATALYSTS

(57) Abstract: Disclosed are electronically perturbed asymmetric aromatic ligands. In one aspect, the ligands are polyfluorinated. The ligands may be nucleophilically substituted. The ligands have many useful applications including catalytic applications. In a preferred aspect, the ligands are polyfluorinated binaphthyl ring derivatives, which are 2,2' dihydroxy or dialkoxy substituted.

Figure 1


OMe
OMe
F
F
F
F
F
F
RO
RO
ROH, Na
reflux
24h
R = Me (84%)
Et (77%)
iPr (89%)
tBu (86%)
Molecular structure of the 7,7'-bis(methoxy) adduct

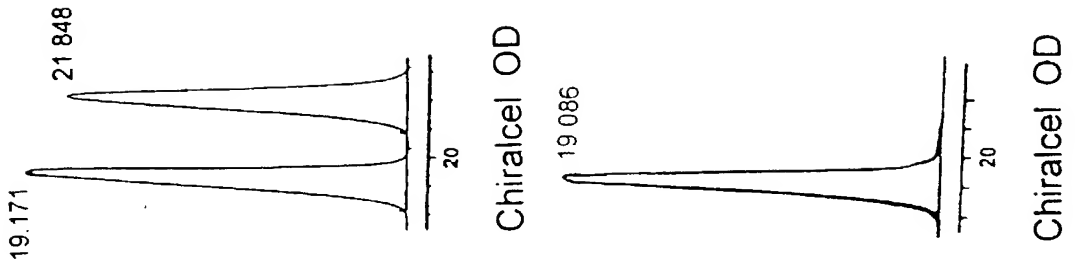

19.171
21.848
20
Chiralcel OD
19.086
20
Chiralcel OD

Figure 2

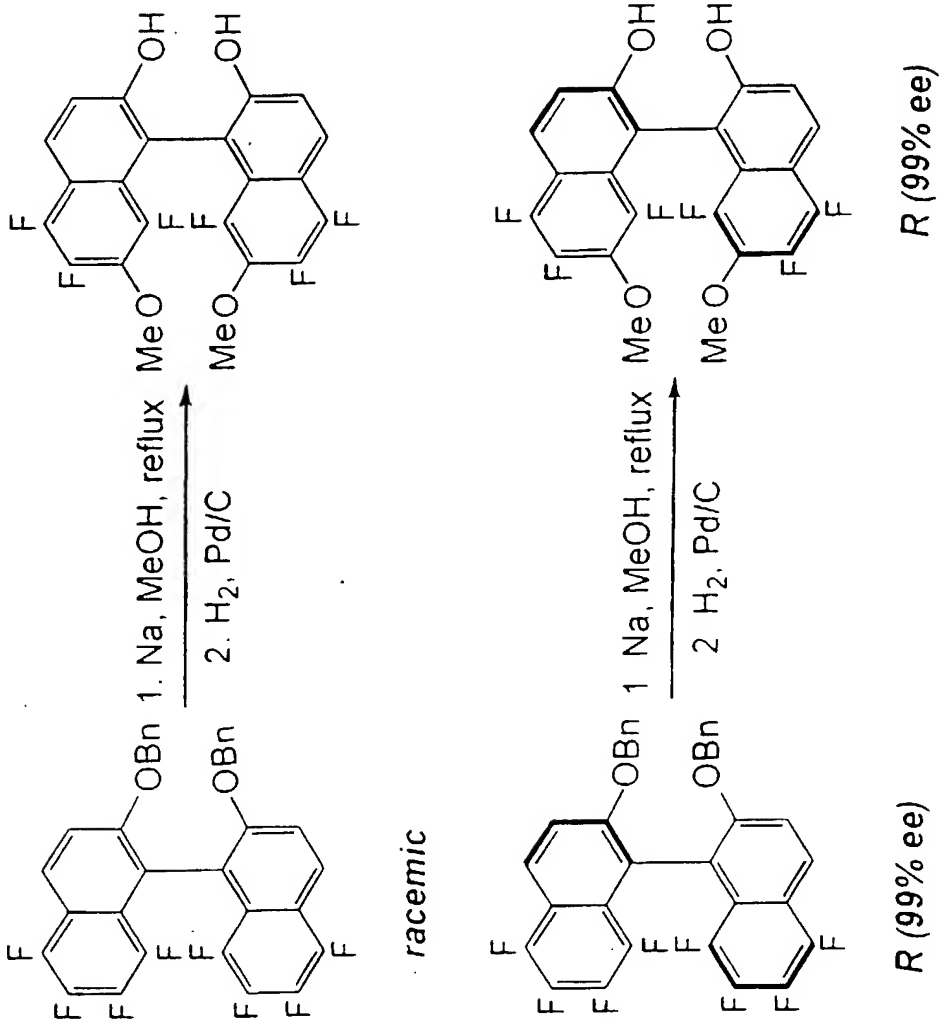

OBn
OBn
1. Na, MeOH, reflux
2. H2, Pd/C
racemic
OH
OH
MeO
MeO
F
R (99% ee)
R (99% ee)

Figure 3

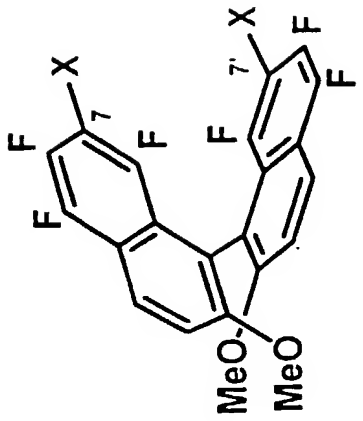
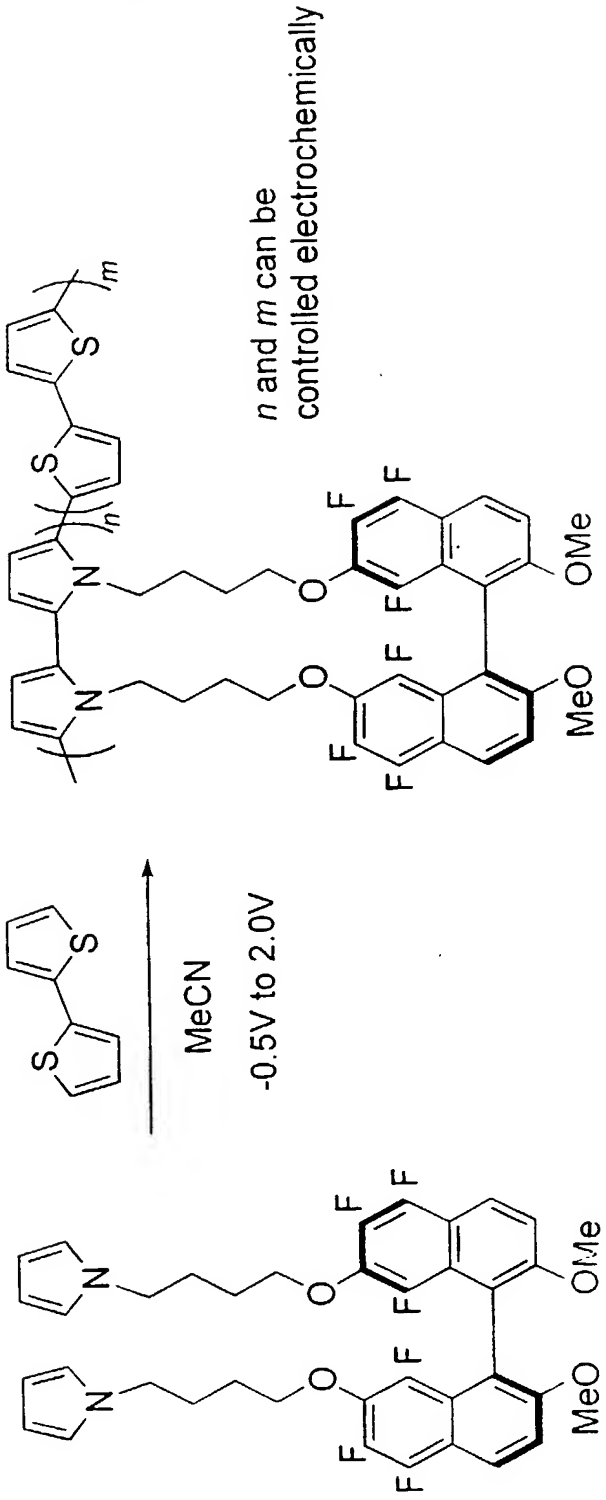


Figure 4


n and m can be
controlled electrochemically
MeCN
-0.5V to 2.0V
OMe
MeO
F
S
N
O

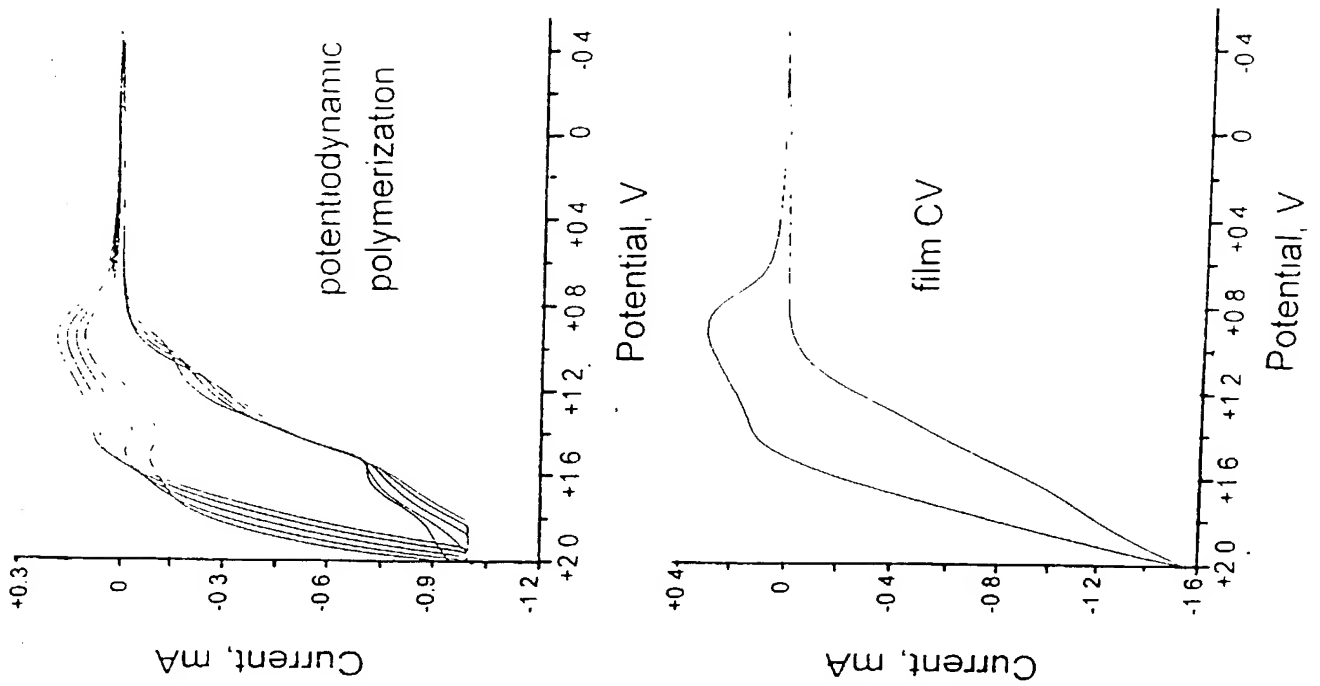
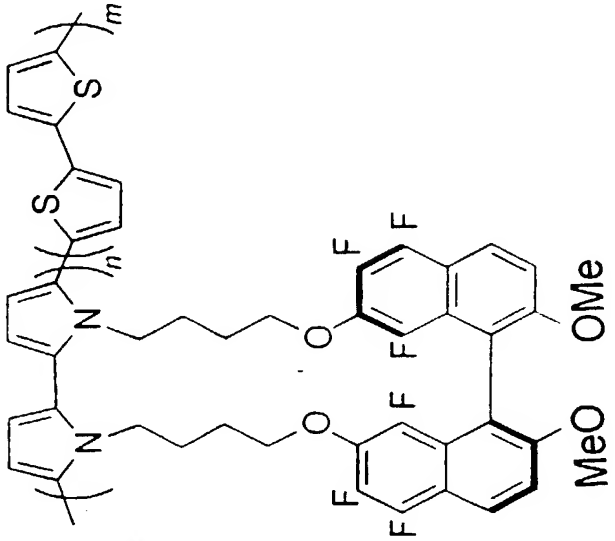
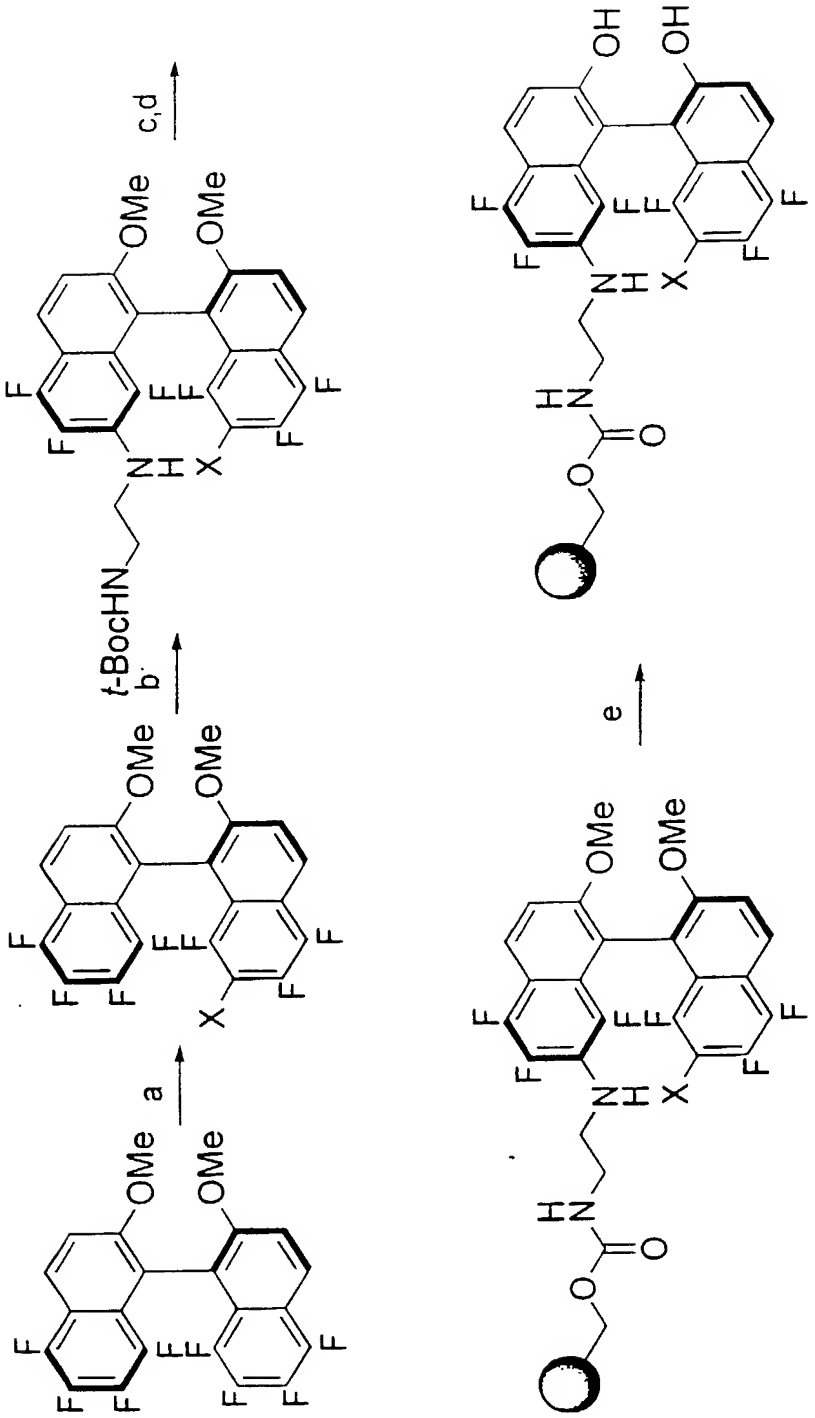


Figure 5



pyrrole/bithiophene
feed ratio: 2:1

Figure 6



Key: a. XH (1 eq), toluene, 100 °C; b. $NH_2CH_2CH_2NH(t\text{-Boc})$, toluene, 100 °C; c. TFA, DCM; d. CDI, THF, TentaGel S OH; e. Pd-C, $HCOONH_4$, MeOH, reflux

Figure 7

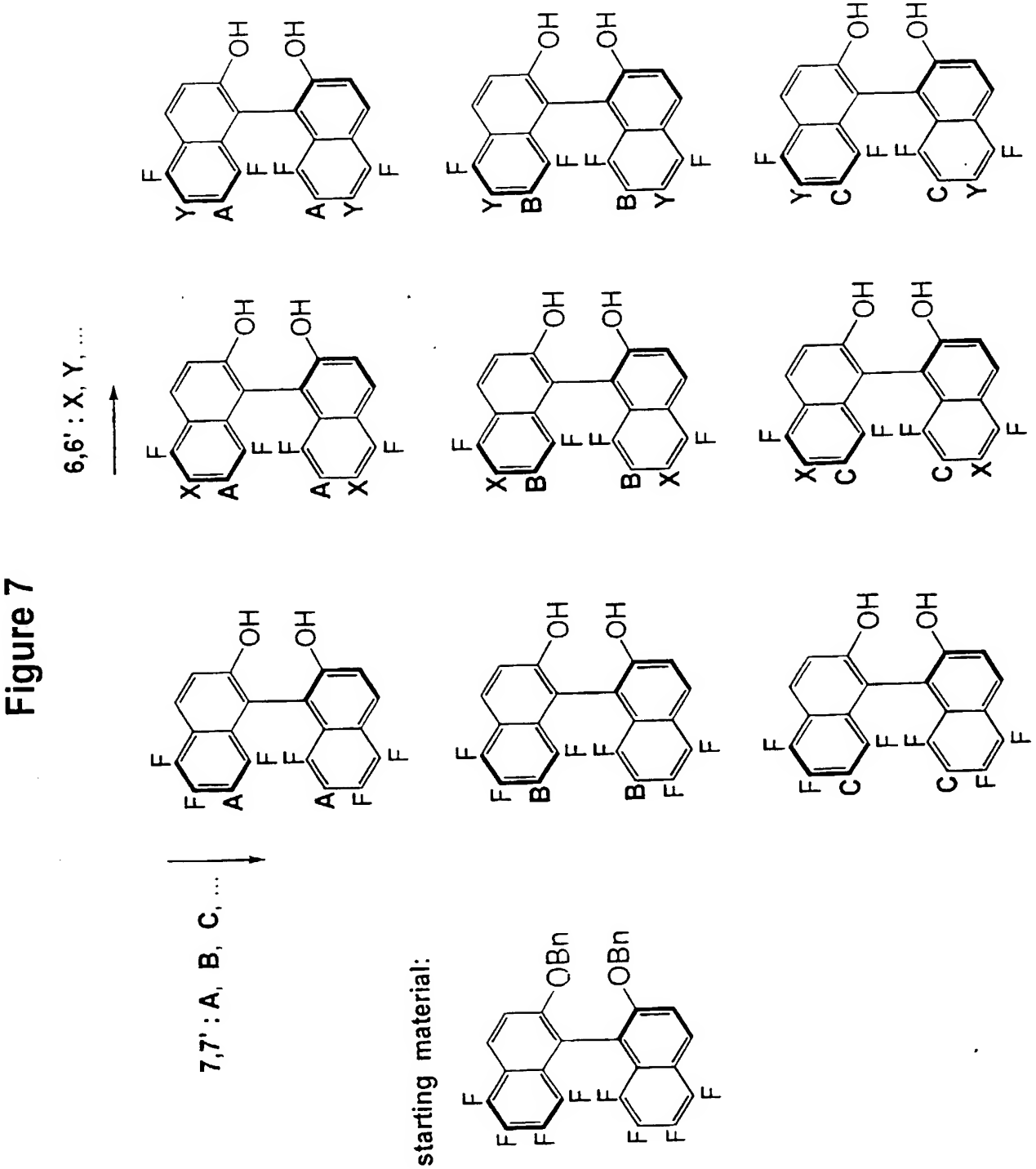


Figure 8

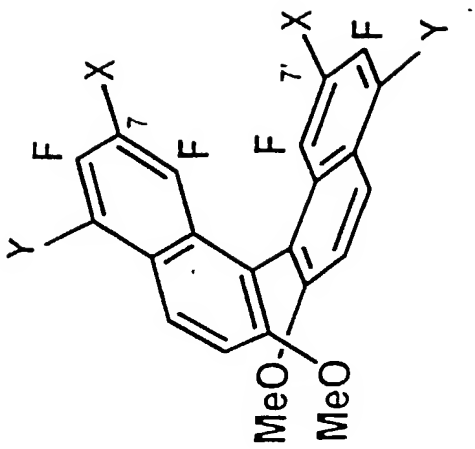


Figure 9

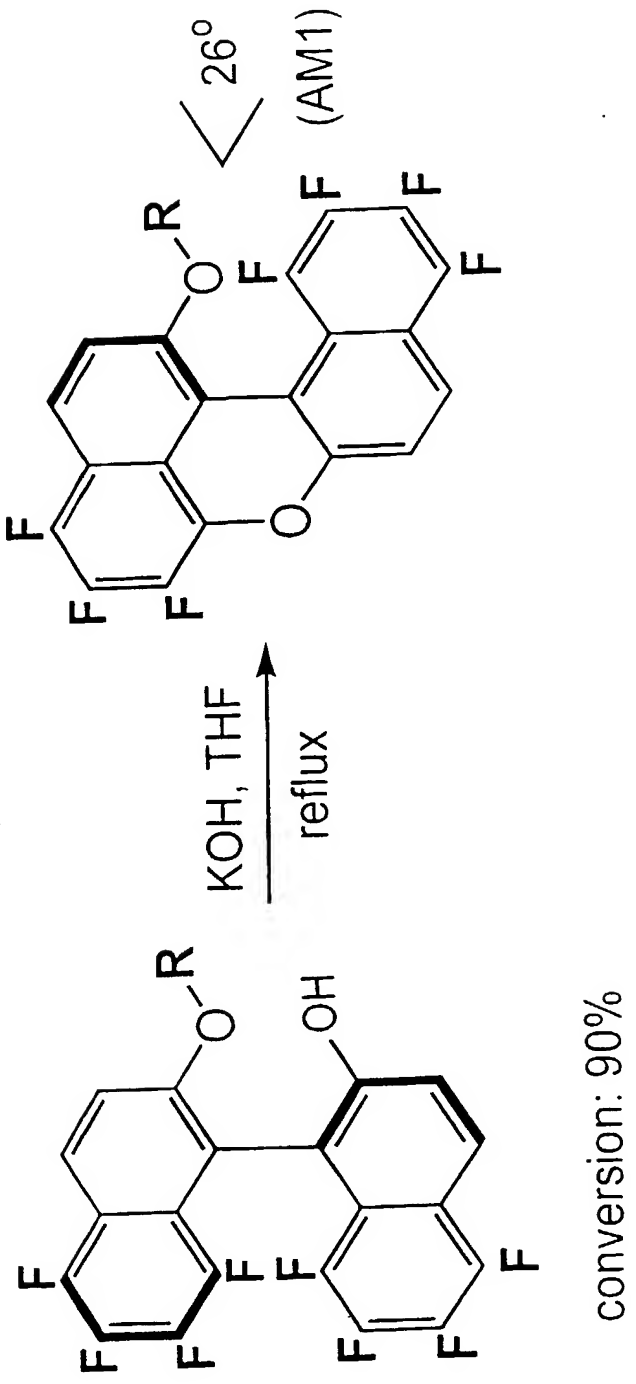
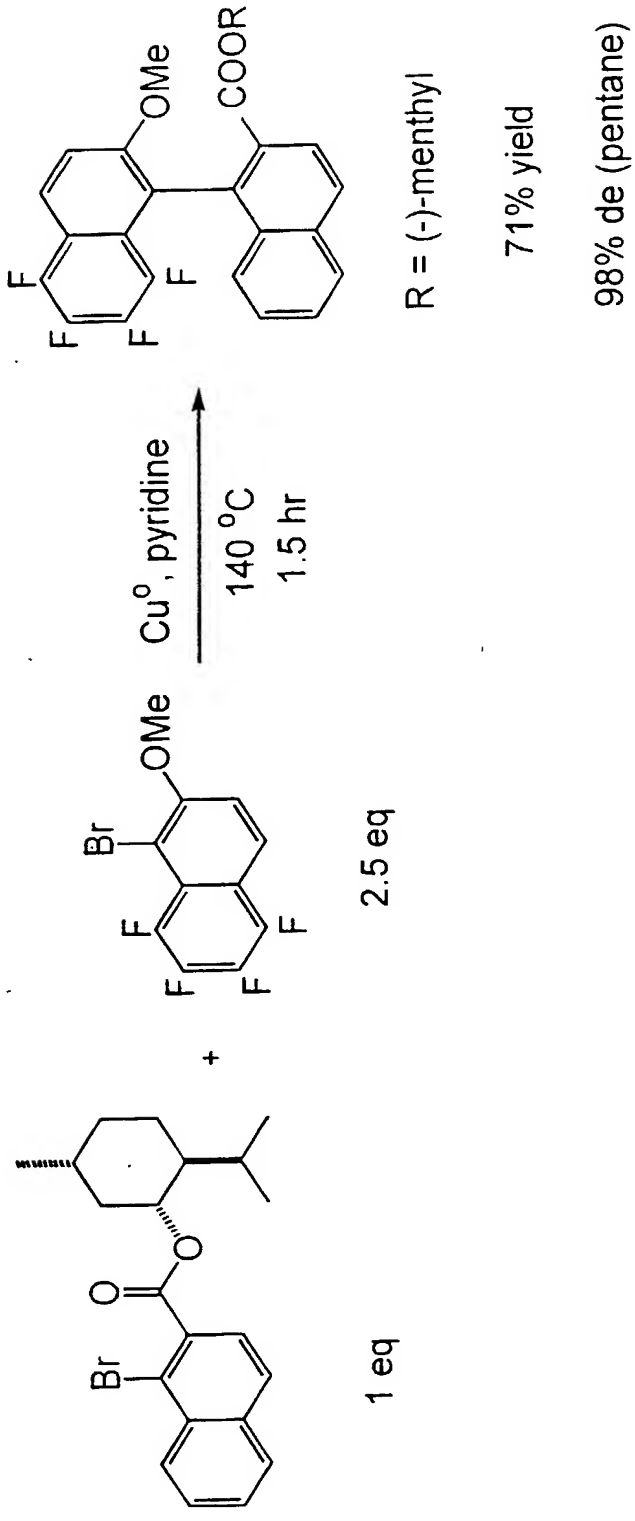


Figure 10


OMe
COOR
F
F
F
F
R = (-)-menthyl
71% yield
98% de (pentane)
Cu°, pyridine
140 °C
1.5 hr
Br
OMe
F
F
F
F
2.5 eq
+
O
O
Br
1 eq

10031449 .092602

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#4.

DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)	Attorney Docket Number	61905/00002
	First Named Inventor	YUDIN, A.
	COMPLETE IF KNOWN	
	Application Number	10/031,449
☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing (surcharge (37 CFR 1.16(e) required)	Filing Date	
	Art Unit	
	Examiner Name	

As the below named inventor, I hereby declare that:

My residence, mailing address, and citizenship are as stated below next to my name.

I believe I am the original and first inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

ASYMMETRIC LIGANDS HAVING USE AS CATALYSTS

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) 07/21/2000 as United States Application Number or PCT International

Application Number PCT/CA00/00850 and was amended on (MM/DD/YYYY) 01/22/2002 (If applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), of 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on supplemental priority data sheet PTO/SB/02B attached hereto:

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DECLARATION — Utility or Design Patent

Direct all correspondence to: ☒ Customer Number or Bar Code Label 27871 OR ☒ Correspondence address below

Name	BLAKE, CASSELS & GRAYDON LLP per Brian W. Gray (Reg. No. 30,017)		
Address	Box 25, Commerce Court West		
Address	199 Bay Street		
City	Toronto	**State** Ontario	**ZIP** M5L 1A9
Country	Canada	**Telephone** 416.863.3256	**Fax** 416.863.2653

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle [if any]) Andrei		**Family Name or Surname** Yudin	
Inventor's Signature X [signature]			**Date** X Sep. 6 '01
Residence: City Toronto CA	**State** Ontario	**Country** Canada	**Citizenship** Canada
Mailing Address 56 Hammersmith Avenue			
Mailing Address			
City Toronto	**State** Ontario	**Zip** M4E 2W4	**Country** Canada

1 -- oo

NAME OF SECOND INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle [if any]) Leo James Patrick		**Family Name or Surname** Martyn	
Inventor's Signature			**Date**
Residence: City Mississauga	**State** Ontario	**Country** Canada	**Citizenship** Canada
Mailing Address 165 - 3349 Mississauga Road			
Mailing Address			
City Mississauga	**State** Ontario	**ZIP** L5L 1J7	**Country** Canada

☒ Additional inventors are being named on the 1 supplemental Additional Inventor(s) sheet(s) PTO/SB/02A attached hereto

(3)

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 1 of 1

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle [if any])	Family Name or Surname		
Subramanian	Pandiaraju		
Inventor's Signature			**Date**
Residence: City St. Laurent	**State** Quebec	**Country** Canada	**Citizenship** Canada
Mailing Address **403** - 600 Cote Vertu			
Mailing Address			
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10051447 .093602

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2-00

NAME OF SECOND INVENTOR:		☐ A petition has been filed for this unsigned inventor	
Given Name (first and middle [if any]) Leo James Patrick		**Family Name or Surname** Martyn	
Inventor's Signature X [signature]			**Date** X July 03/02
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Mailing Address			
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Page 1 of 1

3-00

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Given Name (first and middle [if any])	Family Name or Surname		
Subramanian	Pandiaraju		
Inventor's Signature X S Pandiaraju			**Date** X Aug 28, '02
Residence: City St. Laurent CAX	**State** Quebec	**Country** Canada	**Citizenship** Canada
Mailing Address 403 - 600 Cote Vertu			
Mailing Address			
City St. Laurent	**State** Quebec	**Zip** H4L 5E3	**Country** Canada

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